REMARKS

Discussion of the Amendments

Claims 1-60 are pending. Claims 14, 27, and 60 are withdrawn from consideration. Claim 31 is amended in order to improve readability. Claim 61 is new. Support for the amendment to claim 31 and new claim 61 is found in original claims 4, 17, and 50. No new matter is believed to be added. Upon entry of the amendment, claims 1-61 will be pending.

Remarks Concerning March 27, 2008 Office Action

Applicants' Request for Reconsideration filed January 16, 2008 included reasoning as to why the claims of the present application are patentable in view of U.S. Patent No. 6,506,767 (hereafter "Schumacher") and in view of U.S. patent application 11/283,276.

In the Office Action mailed March 27, 2008, Applicants note that the Office did not formally address Applicants' traversal of the rejection of the elected claims, claims 1-13, 15-26, and 28-59, over Schumacher. Instead, the Office re-iterated the rejection based on U.S. patent application 11/283,276 and raised a new ground of rejection based on U.S. Patent No. 4,659,716 (hereafter "Villani"). Applicants have taken the Office's silence as to Schumacher to mean that this rejection has now been withdrawn, and that the elected claims are patentable over Schumacher.

General Comments

The claimed subject matter is generally directed to solid state forms of the drug desloratadine. In particular, it is concerned with novel and unobvious mixtures of two known polymorphs of desloratadine, designated as Form I and Form II.

The patentability of the claimed subject matter is predicated on, *inter alia*, the unexpected finding that mixtures containing specific ratios of Form I and Form II desloratadine are **stable**, i.e. the ratio of Form I to Form II in such mixtures does not alter with time.

Thus, the claimed mixtures of Form I and Form II desloratadine may advantageously be employed in pharmaceutical compositions to afford dosage forms which exhibit good oral bioavailability, and which are also bioequivalent to commercially available dosage forms containing a single crystalline form of desloratadine.

Rejection over Villani, as evidenced by Schumacher

The Office has taken the position that claims 1-13, 15-26, and 28-59 are inherently anticipated by Villani, as evidenced by Schumacher.

Applicants respectfully traverse this rejection. Applicants believe that this rejection is improper because the Office has not established a *prima facie* case of inherent anticipation. Applicants respectfully request that the Examiner withdraw this rejection after consideration of the following remarks.

Villani discloses at columns 17-18 (Examples V and VI) procedures for preparing crystalline desloratadine, which are reproduced in part below.[1]

EXAMPLE V

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The acetic acid salt prepared as in Example II is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates.

Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°-152° C.

EXAMPLE VI

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridine

B.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]p yridine.

A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°-151° C. After recrystallization from hexane, the product melts at 150°-151° C.

Anal. Calcd. for $C_{19}H_{19}N_2Cl$: C,73.42; H,6.16; N,9.01. Found: C,73.19; H,6.14; N,8.91.

[1] Desloratadine is synonymous with 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and descarboethoxyloratadine.

According to both examples, desloratadine is recrystallized from hexane to afford a product having a melting point of between 150° and 152 °C. Example VI.B contains elemental analysis data for desloratadine but no additional experimental data is given in these examples.

Thus, purely on the basis of the experimental data given in Examples V and VI.B of Villani, it is not possible to conclude whether the desloratadine products described therein constitute a mixture of polymorphs or whether they correspond to a single polymorphic form of desloratadine. The remainder of the specification provides no additional information in this regard.

It is therefore clear that Villani does not provide a clear and unambiguous disclosure of any mixture of polymorphs of desloratadine, let alone a mixture comprising the specific ratios of Form I and Form II as presently claimed. Thus, claims 1-13, 15-26, and 28-59 are considered to be novel over Villani.

In recognition of this deficiency, the Office has taken the position that Schumacher provides additional information lacking in Villani. In particular, the Office has cited Schumacher at column 4, lines 1-4, which recites:

> Descarboxyloratine prepared as described in U.S. Pat. No. 4,659,716 was isolated as the acetic acid salt (Example III) and as a mixture of polymorphs of the free base from hexane (see Examples V+VI).

The Office has assumed that Villani necessarily and inherently discloses the claimed mixture because Schumacher characterizes Villani as disclosing a polymorphic desloratadine mixture. Applicants respectfully disagree with the Office's position at least for the following reasons.

Applicants remind the Office that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."[2] Moreover, the Office is reminded of the legal standard for a finding of inherent

[2] *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). *See also*, MPEP 2131

anticipation, which is explained in MPEP 2112(IV) and is reproduced in part below, with bold-type emphasis supplied:[3]

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities.**

In other words, in order for there to be a sustainable finding of inherent anticipation, the Office must provide evidence and/or scientific reasoning showing that Villani's inherent disclosure *necessarily* describes the presently claimed desloratadine mixtures. Applicants note that even if Schumacher's characterization of Villani is correct, i.e., Villani discloses "a mixture of polymorphs of [desloratadine]," and that the procedures of Examples V and VI.B does afford a mixture of Form I and Form II desloratadine, the Office has failed to establish with any degree of certainty that the mixture so obtained would **inevitably** contain the presently claimed specific ratio(s) of Form I to Form II.

Applicants believe that the Office has not met its burden for a sustainable finding of inherent anticipation by relying on Schumacher's characterization of Villani, i.e., Examples V and VI of Villani affords "a mixture of polymorphs of the free base" of desloratadine.

Thus, as a matter of law, the Office has not met its burden of proof to demonstrate inherent anticipation by an inevitable result. Accordingly, Applicants believe that the Office's position with respect to the presently claimed compositions must be withdrawn.

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[3] *See also Ex parte Havens* 2003 WL 21279863 (BPAI). In *Ex parte Havens*, the Examiner rejected claims directed to delavirdine mesylate in the S and T crystal forms based on inherent anticipation. The BPAI, cited *In re Oelrich* (see above) and found the Examiner's rejection to be premature because the "examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed…is in either the S or T crystal form." A copy of *Ex parte Havens* is found at **Attachment 1**.

Claimed Invention as a Whole is Unobvious over Schumacher

As noted above, the Office did not formally address Applicants' traversal of the rejection of the elected claims, claims 1-13, 15-26, and 28-59, over Schumacher in the Office Action mailed March 27, 2008. In view of this omission, Applicants again summarize the reasons why the claimed desloratadine compositions are unobvious and patentable over Schumacher.

The claimed ranges for the polymorphic mixtures do not "overlap" or "touch" with the polymorphic mixture ranges disclosed in Schumacher. In fact, Schumacher instructs the reader that it is not desirable to use desloratadine polymorphic mixtures in pharmaceutical compositions. For instance, Schumacher discloses that the polymorphic purity of desloratadine should be prepared in "as pure a form as possible," so as to have "constant physical properties," in order to meet the stringent requirements for FDA regulatory approval. *See* Schumacher at column 1, lines 34-41. A fair reading of Schumacher shows that a reason for achieving a certain polymorphic purity for desloratadine is because "a mixture [of polymorphs] could lead to production of a [desloratadine] product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements." *Id.* at column 4, lines 5-11. In other words, Schumacher discloses that desloratadine having the highest possible polymorphic purity, i.e., a single polymorph, is to be preferred over a mixture of polymorphs since the former, having "constant physical properties," is perceived to be more likely to meet FDA Regulatory requirements. Taken this information together, it should be clear that Schumacher teaches away from the presently claimed composition. Applicants also ask that the Office consider the fact that Applicants have discovered unexpectedly, and to the contrary of Schumacher's disclosure, that the presently claimed desloratadine compositions are quite **stable**. *See, e.g.*, Applicants' disclosure at page 13, line 29 – page 14, line 26, which discloses, in part, that the claimed desloratadine compositions / mixtures are **both chemically and polymorphically stable** under certain conditions. For example, Applicants disclose that "[t]he stable mixtures of 25:75, 50:50, 75:25, 84:16 (Form 1:Form 2) do not show any substantial change (Chemical: by degradation; Physical: by transformation to another polymorphic form) in the XRD pattern after exposure at 60%, 80%, 100% RH for one week." *Id.* The fact that Applicants discovered that the presently claimed desloratadine polymorphic mixtures are stable under these conditions is most

unexpected in view of the disclosure of Schumacher. For at least the reasons provided above, Applicants believe that the claimed subject matter is unobvious over Schumacher. Applicants respectfully request that the Office acknowledge the same.

Provisional Rejection based on 11/283,276

The provisional rejection of claims 1-13, 15-26, and 28-59 under the judicially created doctrine of obviousness-type double patenting over claims 21-24 of pending application 11/283,276 ("the '276 application") is respectfully traversed.

Claims 21-24, of the '276 application, are reproduced below:

> 21. A mixture of crystalline Form I and Form II of desloratadine, containing about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof.
>
> 22. The mixture of claim 21, comprising about 35-82% desloratadine Form I and about 18-65% desloratadine Form II.
>
> 23. The mixture of claim 22, comprising about 55-82% desloratadine Form I and about 18-45% desloratadine Form II.
>
> 24. A pharmaceutical formulation comprising the mixture of claim 21.

Although it may be true that claim 21 of the '276 application is directed to crystalline desloratadine comprising a mixture of Form I and Form II, claim 21 of the '276 application also recites that the mixture comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof." This should be contrasted with each of Claims 1, 15, 28, 29, 37, and 49, in which there is no requirement to have a crystalline mixture that comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof."

Applicants kindly request that the Examiner withdraw this rejection.

Request for Rejoinder

Applicants believe that the present application is now in a condition for allowance. In the event that the Examiner acknowledges the same, then Applicants kindly request rejoinder of withdrawn claims 14, 27, and 60.

Procedural Matters

Applicants concurrently filed with the present response a Request for a Three-Month Extension of Time under 37 CFR 1.136(a) with an authorization to charge the requisite fee under 37 CFR 1.17(a)(3) to Applicants' representative Deposit Account 13-2725. If for any reason the Request is separated from the present response, then Applicants authorize the Office to charge the above-noted Deposit Account to pay any necessary fees so as to maintain the pendency of the present application.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

23552
PATENT TRADEMARK OFFICE

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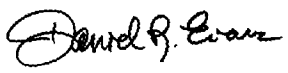

Daniel R. Evans, Ph.D.
Registration No. 55,868

Date: **September 29, 2008**

ATTACHMENT 1

2003 WL 21279863 (Bd.Pat.App. & Interf.)

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences
Patent and Trademark Office (P.T.O.)

EX PARTE JEFFREY L. HAVENS, DONALD P. SMITH, MICHAEL S. BERGREN AND MARK A. LYSTER

Appeal No. 2001-0091
Application No. 08/732,254

NO DATE REFERENCE AVAILABLE FOR THIS DOCUMENT

BRUCE STEIN
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Before WINTERS, ROBINSON, and GRIMES
Administrative Patent Judges
GRIMES
Administrative Patent Judge

ON BRIEF

DECISION ON APPEAL

An oral hearing in this case was scheduled for November 27, 2001. Upon reviewing the case, however, we have determined that an oral hearing will not be necessary and we render the following decision based on the record.

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 and 2. Claims 1 and 2 are directed to specific crystal forms (form "S" and form "T," respectively) of 1-[5-Methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]-piperazine. monomethanesulfonate salt.[FN1] The claims list the powder X-ray diffraction measurements that distinguish the claimed crystal forms from other forms of delavirdine mesylate.

The examiner relies on the following reference:

Palmer et al. (Palmer)	5,563,142	Oct. 8, 1996

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(e) as anticipated by Palmer.

Claims 1 and 2 also stand rejected under 35 U.S.C. § 103 as obvious over Palmer.

Claims 1 and 2 also stand rejected for both statutory and obviousness-type double patenting, based on the claims of Palmer.

We reverse all of the rejections.

Discussion

The claims are directed to delavirdine mesylate in the S crystal form (claim 1) or in the T crystal form (claim 2). The examiner rejected the claims, under several different rationales, over the Palmer patent.

1. Statutory double patenting

The examiner rejected the claims under 35 U.S.C. § 101 "as claiming the same invention as that of claim 11 of prior U.S. Patent No. 5563142." Examiner's Answer, page 4. The examiner explained that "[i]n the absence of evidence showing otherwise, either of the instant claims may be the same compound recited in US'142." Id.

"35 U.S.C. § 101 prevents two patents from issuing on the same invention.... A good test, and probably the only objective test, for 'same invention,' is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention.... If it is determined that the same invention is being claimed twice, 35 U.S.C. § 101 forbids the grant of the second patent." In re Vogel, 422 F.2d 438, 441, 164 USPQ 619, 621-22 (CCPA 1970).

***2** Here, the patent's claim 11 is directed to delavirdine mesylate, without limitation as to crystal form. Instant claims 1 and 2 are directed to delavirdine mesylate in the S and T crystal forms, respectively. Thus, delavirdine mesylate in any crystal form other than S or T, or in a noncrystalline form, would infringe Palmer's claim 11 without infringing either of the claims on appeal. Therefore, the claims on appeal are not directed to the "same invention" as Palmer's claim 11 and are not unpatentable on that basis. The rejection under 35 U.S.C. § 101 is reversed.

2. Anticipation

The examiner rejected the claims under 35 U.S.C. § 102(e) on the basis that "Palmer discloses by name the same chemical compound as the mono methanesulfonate salt. See claim 11 in the US patent. In view of this fact evidence is needed that the prior art compound inherently lacks the characteristics (x-ray diffraction spectra recited in claims 1 and 2) relied on herein." Examiner's Answer, page 3.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "An inherent structure, composition or function is not necessarily known.... Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

"'Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) (quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)). When the inherent properties of a prior art product are at issue, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. Ex parte Skinner, 2 USPQ2d 1788, 1789 (Bd. Pat. App. Int. 1986).

Here, the claims on appeal are not directed to delavirdine mesylate per se, but are limited to the S and T crystal forms of that compound. Therefore, to anticipate the claims, the prior art must disclose delavirdine mesylate in the S and T crystal forms. The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed

by Palmer is in either the S or T crystal form. Therefore, the examiner has not made out a prima facie case of anticipation by inherency.

***3** The examiner's attempt to shift the burden of proof to Appellants was premature. The burden shifts to the applicant only if the examiner can show, by evidence or scientific reasoning, a reasonable basis for concluding that the prior art product meets all the limitations of the claims. The examiner has provided no basis for such a conclusion in this case. The rejection under 35 U.S.C. § 102 is reversed.

3. Obviousness

The examiner rejected the claims under 35 U.S.C. § 103 on the basis that Palmer "discloses the free form of the instant sulfonate salts for use in treating HIV." Examiner's Answer, page 3. The examiner concluded that the corresponding methanesulfonate salt would have been an obvious variant because Palmer "teaches and in fact prefers the use of salt forms for better solubility and crystallinity," and methanesulfonate salts were exemplified for compounds other than delavirdine mesylate. Id., pages 3-4.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection, namely, that it is directed to delavirdine mesylate per se, rather than to the specific S and T crystal forms of delavirdine mesylate that are the subject of the claims on appeal. The examiner has provided no evidence or convincing reasoning why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.

Nor has the examiner established that Palmer would have enabled those skilled in the art to make the claimed S and T crystal forms of delavirdine mesylate. Appellants' specification discloses specific conditions for recrystallizing delavirdine mesylate that produce the S and T crystal forms. See pages 2-4 and Examples 1-8. Palmer does not disclose or suggest even the existence of the S and T crystal forms of delavirdine mesylate, let alone how to make them. As stated in In re Hoeksema:

> [I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

***4** 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968) (footnote omitted).

Since the examiner has not established that Palmer would have rendered the claimed invention obvious to those skilled in the art, she has not made out a prima facie case under 35 U.S.C. § 103. The rejection for obviousness is reversed.

4. Obviousness-type double patenting

The examiner rejected the claims for obviousness-type double patenting over Palmer's claim 11. The examiner argues that the instant claims and Palmer's claim 11 are not patentably distinct because they contain "overlapping subject matter" and because Palmer also claims the free form of delavirdine, which is an obvious variant of delavirdine mesylate. Examiner's Answer, page 4.

> Obviousness-type double patenting … requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. Its purpose is to prevent an unjustified extension of the term of the right to exclude granted by a patent by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner later.

In re Berg, 140 F.3d 1428, 1431, 46 USPQ2d 1226, 1229 (Fed. Cir. 1998) (citation omitted, emphasis added).

> All proper double patenting rejections, of either type, rest on the fact that a patent has been issued and later issuance of a

> second patent will continue protection, beyond the date of expiration of the first patent, of the very same invention claimed therein (same invention type double patenting) or of a mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art (obviousness-type double patenting). In the latter case, there must be some clear evidence to establish why the variation would have been obvious.

In re Kaplan, 789 F.2d 1574, 1579-80, 229 USPQ 678, 683 (Fed. Cir. 1986) (emphasis in original).

Thus, a proper rejection for obviousness-type double patenting requires showing that the later-claimed subject matter "would have been obvious to those of ordinary skill in the relevant art" based on the claims in the earlier patent. As discussed above, the examiner has pointed to nothing in either the claims or the disclosure of the Palmer patent that would have suggested the S and T crystal forms of delavirdine mesylate to a person of ordinary skill in the art. We therefore reverse the rejection for obviousness-type double patenting.

Summary

We reverse all of the rejections because the examiner has not established that the prior art disclosed or suggested the claimed S and T crystal forms of delavirdine mesylate.

REVERSED

BOARD OF PATENT APPEALS AND INTERFERENCES

***5** SHERMAN D. WINTERS

Administrative Patent Judge

DOUGLAS W. ROBINSON

Administrative Patent Judge

ERIC GRIMES

Administrative Patent Judge

FN1. This compound is also known as delavirdine mesylate, Appeal Brief, page 2, and we will refer to it as such.

2003 WL 21279863 (Bd.Pat.App. & Interf.)
END OF DOCUMENT